

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P/23766.WO/ICB	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 03067	International filing date (day/month/year) 09/08/2000	(Earliest) Priority Date (day/month/year) 12/08/1999
Applicant ANGIOGENE PHARMACEUTICALS LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03067

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C43/23 A61K31/09 A61P35/00 C07F9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 48590 A (ANGIOGENE PHARMACEUTICALS) 24 August 2000 (2000-08-24) claims 2,14; example 4 ---	1-5,9,10
A	M. CUSHMAN: "Synthesis and evaluation of stilbene and dihydrostilbene derivatives as potential anticancer agents that inhibit tubulin polymerization" JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, 1991, pages 2579-2588, XP000571676 WASHINGTON US cited in the application tables I,V --- -/--	1,5,9,10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

30 March 2001

Date of mailing of the international search report

27/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Wright, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>K. OHSUMI: "Novel combretastatin analogues effective against murine solid tumors: design and structure-activity relationships" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, 1998, pages 3022-3032, XP002102895 WASHINGTON US cited in the application tables 1-6</p>	1,5,9,10
A	<p>--- J. A. WOODS: "The interaction with tubulin of a series of stilbenes based on combretastatin A-4" BRITISH JOURNAL OF CANCER, vol. 71, 1995, pages 705-711, XP000978556 cited in the application page 707, column 2 -page 710, column 2</p>	1,5,9,10
A	<p>--- US 5 561 122 A (G. R. PETTIT) 1 October 1996 (1996-10-01) claims</p>	1,5,9,10
A	<p>--- EP 0 641 767 A (AJINOMOTO) 8 March 1995 (1995-03-08) example 8; table 1</p>	1,5,9,10
A	<p>--- WO 92 16486 A (ASTON MOLECULES) 1 October 1992 (1992-10-01) claims; examples</p>	1,5,9,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

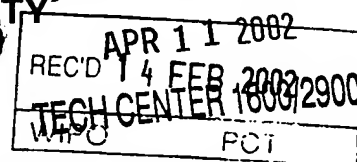
International Application No

PCT/GB 00/03067

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0048590	A	24-08-2000	AU 2558300 A	04-09-2000
US 5561122	A	01-10-1996	NONE	
EP 641767	A	08-03-1995	AT 174899 T	15-01-1999
			CA 2131683 A	09-03-1995
			CN 1105967 A,B	02-08-1995
			DE 69415445 D	04-02-1999
			DE 69415445 T	22-07-1999
			DK 641767 T	23-08-1999
			ES 2126068 T	16-03-1999
			GR 3029603 T	30-06-1999
			JP 3045017 B	22-05-2000
			JP 7228558 A	29-08-1995
			SI 641767 T	30-04-1999
			US 5525632 A	11-06-1996
			US 5731353 A	24-03-1998
WO 9216486	A	01-10-1992	AU 1371992 A	21-10-1992

PCT

RECEIVED



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/049248

Applicant's or agent's file reference P/23766.WO/ICB	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/03067	International filing date (day/month/year) 09/08/2000	Priority date (day/month/year) 12/08/1999
International Patent Classification (IPC) or national classification and IPC C07C43/23		
Applicant ANGIOGENE PHARMACEUTICALS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 07/03/2001	Date of completion of this report 12.02.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Wright, M Telephone No. +31 70 340 3124 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03067

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*):

Description, pages:

1-14 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03067

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-10
	No: Claims
Inventive step (IS)	Yes: Claims 1-10
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-10
	No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The compounds according to claims 1-8 are not disclosed in the prior art; they differ from prior art analogues by virtue of the combination of substituents at C-3 and C-4 of the B-ring. Claims 9 and 10 also relate to novel subject-matter.

The prior art teaches that replacement of the 4-methoxy group in the B-ring of combretastatin A-4 analogues by other substituents results in a reduction of cytotoxicity. The modified combretastatins of the present invention are thus not obvious to the skilled person and the reduction in functional vascular volume demonstrated could not have been predicted.

The requirements of Article 33(2) and (3) PCT are met.

Re Item VI

Certain documents cited

WO-A-0048590, published on 24.08.2000 and claiming priority from GB 9903403 of 16.02.99, discloses (see example 4) a nitro arginine derivative of the compound according to claim 1 of the present application in which R¹, R², and R³ are methyl, R⁵ is H and R⁴ is methyl.

Re Item VIII

Certain observations on the international application

The definition of alkyl, alone or in combinations, according to page 4, lines 1-4 of the description casts doubt on the scope of claims 1-3, 5-7, 9 and 10, which place no limitation on the meaning of alkyl. The claims should be clear without having to refer to the description (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 11 April 2001 (11.04.01)	
International application No. PCT/GB00/03067	Applicant's or agent's file reference P/23766.WO/ICB
International filing date (day/month/year) 09 August 2000 (09.08.00)	Priority date (day/month/year) 12 August 1999 (12.08.99)
Applicant DAVIS, Peter, David	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
07 March 2001 (07.03.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
--	--

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P/23766.WO/ICB	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
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6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03067

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C43/23 A61K31/09 A61P35/00 C07F9/12

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Minimum documentation searched (classification system followed by classification symbols)

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BEILSTEIN Data, CHEM ABS Data

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *G* document member of the same patent family

Date of the actual completion of the international search

30 March 2001

Date of mailing of the international search report

27/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Wright, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03067

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	✓US 5 561 122 A (G. R. PETTIT) 1 October 1996 (1996-10-01) claims -----	1,5,9,10
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INTERNATIONAL SEARCH REPORT

Information on patent family members.

International Application No

PCT/GB 00/03067

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0048590	A	24-08-2000	AU	2558300 A	04-09-2000
US 5561122	A	01-10-1996	NONE		
EP 641767	A	08-03-1995	AT	174899 T	15-01-1999
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			CN	1105967 A, B	02-08-1995
			DE	69415445 D	04-02-1999
			DE	69415445 T	22-07-1999
			DK	641767 T	23-08-1999
			ES	2126068 T	16-03-1999
			GR	3029603 T	30-06-1999
			JP	3045017 B	22-05-2000
			JP	7228558 A	29-08-1995
			SI	641767 T	30-04-1999
			US	5525632 A	11-06-1996
			US	5731353 A	24-03-1998
WO 9216486	A	01-10-1992	AU	1371992 A	21-10-1992

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 February 2001 (22.02.2001)

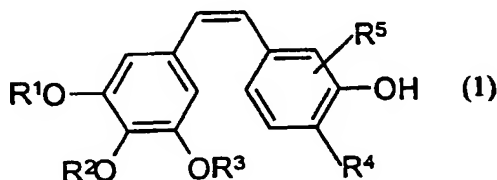
PCT

(10) International Publication Number
WO 01/12579 A3

- (51) International Patent Classification⁷: C07C 43/23, A61K 31/09, A61P 35/00, C07F 9/12
- (21) International Application Number: PCT/GB00/03067
- (22) International Filing Date: 9 August 2000 (09.08.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9918912.8 12 August 1999 (12.08.1999) GB
- (71) Applicant (for all designated States except US): AN-GIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5S (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Watlington OX9 5SX (GB).
- (74) Agents: BAILLIE, Iain, C. et al.; Langner Parry, 52-54 High Holborn, London WC1V 6RR (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- (88) Date of publication of the international search report:
11 October 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/12579 A3

(54) Title: NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY



(57) Abstract: A group of novel cis-stilbenes as disclosed of formula (1) wherein: R¹, R² and R³ are each independently alkyl, R⁴ is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo, R⁵ is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo, or a pharmaceutically acceptable salt thereof or a prodrug such as a phosphate ester. These compounds have vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularisation may have therapeutic benefit.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/00/03067

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C43/23 A61K31/09 A61P35/00 C07F9/12

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07F A61K

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BEILSTEIN Data, CHEM ABS Data

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- *O* document referring to an oral disclosure, use, exhibition or other means
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

B document member of the same patent family

Date of the actual completion of the international search

30 March 2001

Date of mailing of the international search report

27/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Wright, M

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/90/03067

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	K. OHSUMI: "Novel combretastatin analogues effective against murine solid tumors: design and structure-activity relationships" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, 1998, pages 3022-3032, XP002102895 WASHINGTON US cited in the application tables 1-6	1,5,9,10
A	--- J. A. WOODS: "The interaction with tubulin of a series of stilbenes based on combretastatin A-4" BRITISH JOURNAL OF CANCER, vol. 71, 1995, pages 705-711, XP000978556 cited in the application page 707, column 2 -page 710, column 2	1,5,9,10
A	--- US 5 561 122 A (G. R. PETTIT) 1 October 1996 (1996-10-01) claims	1,5,9,10
A	--- EP 0 641 767 A (AJINOMOTO) 8 March 1995 (1995-03-08) example 8; table 1	1,5,9,10
A	--- WO 92 16486 A (ASTON MOLECULES) 1 October 1992 (1992-10-01) claims; examples	1,5,9,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0048590	A	24-08-2000	AU 2558300 A	04-09-2000
US 5561122	A	01-10-1996	NONE	
EP 641767	A	08-03-1995	AT 174899 T	15-01-1999
			CA 2131683 A	09-03-1995
			CN 1105967 A,B	02-08-1995
			DE 69415445 D	04-02-1999
			DE 69415445 T	22-07-1999
			DK 641767 T	23-08-1999
			ES 2126068 T	16-03-1999
			GR 3029603 T	30-06-1999
			JP 3045017 B	22-05-2000
			JP 7228558 A	29-08-1995
			SI 641767 T	30-04-1999
			US 5525632 A	11-06-1996
			US 5731353 A	24-03-1998
WO 9216486	A	01-10-1992	AU 1371992 A	21-10-1992

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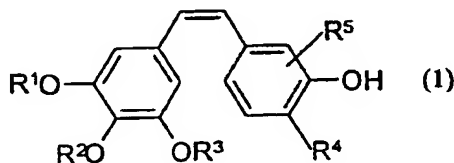
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- (71) Applicant (for all designated States except US): AN-GIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5S (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Watlington OX9 5SX (GB).
- (74) Agents: BAILLIE, Iain, C. et al.; Langner Parry, 52-54 High Holborn, London WC1V 6RR (GB).
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WO 01/12579 A3

(54) Title: NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY



(57) Abstract: A group of novel cis-stilbenes as disclosed of formula (1) wherein: R¹, R² and R³ are each independently alkyl, R⁴ is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo, R⁵ is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo, or a pharmaceutically acceptable salt thereof or a prodrug such as a phosphate ester. These compounds have vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularisation may have therapeutic benefit.

INTERNATIONAL SEARCH REPORT

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 PCT/00/03067

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07C43/23 A61K31/09 A61P35/00 C07F9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07C C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 48590 A (ANGIOGENE PHARMACEUTICALS) 24 August 2000 (2000-08-24) claims 2,14; example 4 ---	1-5,9,10
A	M. CUSHMAN: "Synthesis and evaluation of stilbene and dihydrostilbene derivatives as potential anticancer agents that inhibit tubulin polymerization" JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, 1991, pages 2579-2588, XP000571676 WASHINGTON US cited in the application tables I,V --- -/--	1,5,9,10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Wright, M

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INTERNATIONAL SEARCH REPORT

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			US	5525632 A	11-06-1996
			US	5731353 A	24-03-1998
WO 9216486	A	01-10-1992	AU	1371992 A	21-10-1992

NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

- Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.
- Compounds able to damage neovasculature have advantages in the treatment of disease. For example, attacking tumour vasculature has several important advantages over a direct attack on the tumour. In particular the endothelial cells of tumour vasculature are more genetically stable than those of the tumour itself and are therefore less likely to become resistant to the damaging agent. Thus a major problem in conventional anti-tumour chemotherapy, that of drug resistance, is circumvented by this approach. Furthermore, since the endothelial cells of the tumour vasculature, unlike the tumour cells themselves, are similar between different solid tumour types, vascular damaging agents are able to attack a wide range of tumour types.
- A number of tubulin-binding agents including the stilbenes combretastatin A1, combretastatin A4 (D. J. Chaplin *et al.*, British J. Cancer 27, S86-S88 (1996)) and combretastatin A4 phosphate (D.J. Chaplin *et al.*, Anticancer Research 19, 189-196, (1999)) are known to selectively damage neovasculature of solid tumours in animal models. While there are reports of the activity of other analogues of combretastatin A4 in tubulin binding assays, in cytotoxicity assays and in tumour models there have been no reports of the vascular damaging activities of analogues. Since the activity of

tubulin-binding compounds against *in vitro* assays are poor predictors of selective vascular damaging activity and activity of such compounds *in vivo* can also be mediated by direct antimitotic effects on the tumour itself, no prediction can be made of the selective vascular damaging activity of known or novel analogues of the combretastatins from published reports. Thus compounds which have the advantages of a selective anti-vascular mechanism given above, rather than acting through a direct effect on the tumour tissue itself, are not apparent.

We have found a series of novel *cis*-stilbenes with vascular damaging activity. These compounds specifically damage newly-formed vascular endothelium, especially that associated with solid tumours, without affecting the normal, established vascular endothelium of the host species. Such compounds are of use in the prophylaxis and treatment of cancers involving solid tumours and in other diseases where there is inappropriate formation of new vasculature such as diabetic retinopathy, psoriasis, rheumatoid arthritis, macular degeneration and the formation of atherosclerotic plaques.

Known vascular-damaging stilbenes, combretastatin A1, combretastatin A4 and combretastatin A4 phosphate have a 4-methoxy group in the "B" ring. The compounds of the invention lack a 4-methoxy group in the ring corresponding to the "B" ring of combretastatin A4. Several studies suggest that substituting alternative groups for the 4-methoxy group in the B-ring of combretastatin A4 would considerably reduce biological activity:

In J. Med. Chem 1991, 34, 2579-2588, Cushman *et al.* state, regarding analogues of combretastatin A4: "the presence of a 4-methoxy group in the B-ring plays a very important role for this compound to be highly cytotoxic". Replacement of the 4-methoxy group with chlorine, for example, gave compounds that were three to four orders of magnitude less potent against a panel of five different cell lines.

In J. Med. Chem. 1998, 41, 3022-3032 Ohsumi *et al.* disclose anilino analogues of combretastatin A4 in which the replacement of the B-ring 4-methoxy group by either a methyl group or a chlorine atom gave a reduction in biological potency of 8.5-fold and 13.5-fold respectively.

5

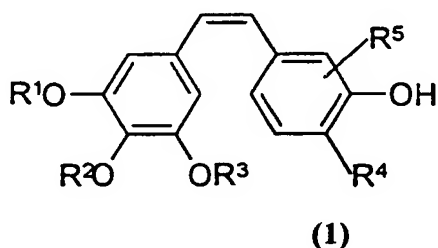
Similarly in Brit. J. Cancer 1995, 71, 705-711 Woods *et al.* disclose analogues of combretastatin with reduced potency. For example the 4-methyl compound shows 3.5 to 36-fold reduction in potency against four cell lines compared to the 4-methoxy compound.

10

It cannot be anticipated from the above studies that compounds in which the B-ring 4-methoxy group is replaced would retain anti-vascular activity. It is particularly unexpected that replacing the B-ring methoxy group of combretastatin A4 would result in a compound with similar potency as a vascular damaging agent.

15

Thus according to one aspect of the invention we provide a compound of formula (1):



20

Wherein:

R¹, R² and R³ are each independently alkyl,

25 R⁴ is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo,

R⁵ is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo,

and the pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

As used herein the term "alkyl", alone or in combinations, means a straight or branched-chain alkyl group containing from one to seven, preferably a maximum of four, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

An alkenyl group may be for example an olefinic group containing from two to seven carbon atoms for example methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene and t-butylene. An alkynyl group may be for example an ethynyl, propynyl or butynyl group.

Where one or more functional groups in compounds of formula (1) are sufficiently basic or acidic the formation of salts is possible. Suitable salts include pharmaceutically acceptable salts for example acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates, salts derived from inorganic bases including alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and salts derived from organic amines such as morpholine, piperidine or dimethylamine salts.

Prodrugs of the invention are compounds which upon administration to a mammal produce compounds of formula (1). Such prodrugs can be for example converted within the mammal by hydrolysis. Prodrugs are preferably ester derivatives of the phenolic hydroxy group contained in compounds of formula (1) such as, for example, phosphate esters, carboxylate esters, sulphate esters and carbonates.

Preferred compounds of the invention are those of formula 1 in which R^1 , R^2 and R^3 are all methyl, and prodrugs thereof

Further preferred compounds of the invention are those of formula 1 in which R¹, R² and R³ are all methyl and R⁵ is hydrogen and prodrugs thereof

- 5 Still further preferred compounds of the invention are those of formula 1 in which R¹, R² and R³ are all methyl, R⁵ is hydrogen and R⁴ is alkyl or halo and prodrugs thereof

Preferred prodrugs of the invention are phosphate esters. Particularly preferred prodrugs of the invention are dihydrogen phosphate esters.

10

Specifically preferred compounds of the invention are:

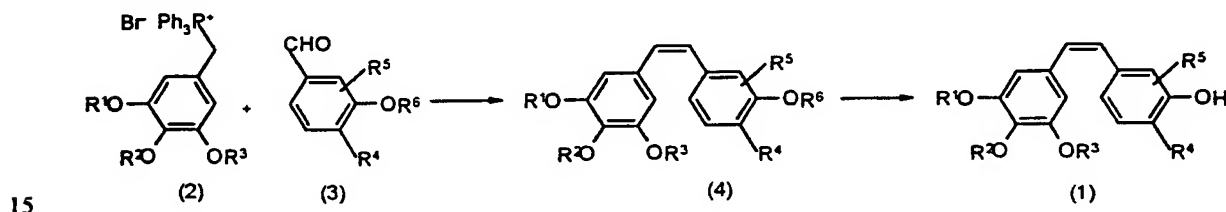
(Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

- 15 (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate

Compounds of the invention can be prepared by any process known to a person skilled in the art. Compounds of formulae (1) can be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In
20 the general preparations described below it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. In the following process description, the symbols R¹, R², R³, R⁴ and R⁵, when used in the formulae depicted are to be
25 understood to represent those groups described above in relation to formula (1) unless otherwise indicated

In one general example compounds of formula (1) can be prepared by Wittig olefin synthesis involving reaction of a phosphonium salt of formula (2) with a strong base,
30 for example an alkyl lithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether

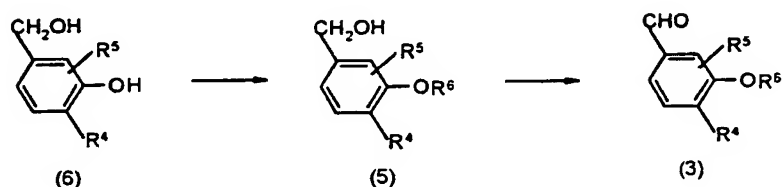
or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 30°C followed by treatment with an aldehyde of formula (3) in which R⁶ is a protecting group, to give an intermediate of formula (4). The synthesis of compounds of formula (1) is then completed by removal of the group R⁶. Suitable protecting groups R⁶ include trialkylsilyl, for example t-butyl-
 5 butyldimethylsilyl, and allyl. Where R⁶ is a trialkylsilyl group it may be removed, for example, by treatment with a quaternary ammonium fluoride such as tetrabutylammonium fluoride in an ether solvent such as tetrahydrofuran at a temperature of about -30°C to about 40°C conveniently at or near ambient
 10 temperature. Where R⁶ is an allyl group it may be removed for example by treatment with a palladium(0) complex such as tetrakis(triphenylphosphine)Pd(0) in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of about -40°C to about 40°C conveniently at or near ambient temperature, in the presence of an allyl scavenger such as morpholine.



Aldehydes of formula (3) can be prepared by any process known to a person skilled in the art. In one general example an aldehyde of formula (3) can be prepared from an alcohol of formula (5) by oxidation with a suitable oxidising agent. Suitable oxidising
 20 agents include the Dess-Martin reagent and manganese dioxide. Alcohols of formula (5) can be prepared by application of standard methods of organic synthesis including the selective protection of phenols of formula (6). Where the protecting group R⁶ is a trialkylsilyl group, for example t-butyl-
 25 butyldimethylsilyl, alcohols of formula (5) may be prepared, for example, by treatment of a phenol of formula (6) with a strong base, for example an alkylolithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a

temperature of between about -100°C to about 40°C followed by treatment with *tert*-butylchlorodimethylsilane.

Phenols of formula (6) are either known or may be prepared from known compounds using standard methods of organic synthesis.



Compounds of formula (1) may also be prepared from other compounds of formula (1) by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, halogenation, oxidation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents.

Prodrugs of compounds of formula (1) can be prepared by any process known to a person skilled in the art. Processes for the preparation of prodrugs of compounds of formula 1 include standard acylation, sulphation and phosphorylation reactions. In one general example dihydrogen phosphate esters of compounds of formula (1) can be prepared by treatment of the corresponding di-*t*-butylphosphate esters with an acid, for example hydrochloric acid or trifluoroacetic acid, in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of from about -20°C to about 40°C, conveniently at room temperature.

Compounds according to the invention are able to destroy tumour vasculature and vasculature that has been newly formed while leaving unaffected normal, mature vasculature. The ability of the compounds to act in this way may be determined by the tests described hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

5

The compounds of the invention may be administered as a sole therapy or in combination with other treatments. Thus the invention includes compositions for the treatment of neovascularisation which compositions contain an effective amount of a cis-stilbene or prodrugs thereof as hereinbefore defined. The invention also includes

10 the use in the preparation of a composition for the treatment of neovascularisation of a cis-stilbene or prodrugs thereof as hereinbefore defined. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, vincristine, vinorelbine,

15 paclitaxel and docetaxel; platinum derivatives for example cisplatin and carboplatin; alkylating agents, for example melphalan, chlorambucil, busulphan, ifosfamide and cyclophosphamide; antimetabolites, for example methotrexate, 5-fluorouracil, cytosine arabinoside, gemcitabine and hydroxyurea; antitumour antibiotics for example bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C,

20 dactinomycin and mithramycin; enzymes, for example asparaginase; topoisomerase inhibitors for example etoposide, teniposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab and trastuzumab; anti-hormones for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene, anastrozole,

25 letrozole, vorazole, exemestane, flutamide, nilutamide and bicalutamide; anti-growth factor compounds for example EGFr tyrosine kinase inhibitors VEGFr kinase inhibitors and PDGFr tyrosine kinase inhibitors; and anti-angiogenesis agents such as angiostatin, endostatin and thalidomide. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

30

For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, 5 rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal 10 administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a 15 particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.1 to 10mg/kg.

20

BIOLOGICAL ACTIVITY

The following test was used to demonstrate the activity of compounds according to the invention.

25

Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using 30 the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). At least three animals were used in control and treated

groups. The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μ m sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels. Examples of the activity of compounds of the invention in this test are given in the table:

Compound of Example	Dose (mg/kg)	% Reduction in Functional Vascular Volume
1	50	88
3	50	27
5	50	20

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

(Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

A solution of 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (491mg) in anhydrous tetrahydrofuran (10ml) at room temperature was treated slowly with a 1.1M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1ml). After 30 minutes crushed ice (5ml) and diethylether (30ml)

were added and the aqueous phase extracted with diethylether (5 portions of 5ml).

The combined extracts were washed with water (3 portions of 10ml) and brine (10ml), dried (MgSO₄) and concentrated under reduced pressure to give a solid.

Recrystallisation from ethyl acetate/hexane gave the title compound (208mg) as a
5 white solid m.p. 123-125°C. nmr: δ H (500MHz, d₆-DMSO) 2.07 (s, 3H), 3.57 (s, 6H), 3.62 (s, 3H), 6.40 (d, J = 12Hz, 1H), 6.46 (d, J = 12 Hz, 1H), 6.56 (s, 2H), 6.61 (dd, J = 8Hz, 2Hz, 1H), 6.76 (d, J= 1.7Hz, 1H), 6.98 (d, J = 8Hz, 1H), 9.21 (s 1H).

The 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
10 used as starting material in the above preparation was prepared as follows:

A suspension of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (848mg) in dry tetrahydrofuran (50ml) at -78°C was treated dropwise with n-butyllithium (0.9ml of a 1.8M solution in hexane) and the mixture allowed to warm to -40°C and stir for 1h.

The mixture was recooled to -78°C and a solution of 3-*tert*-butyldimethylsilyloxy-4-
15 methylbenzaldehyde (390mg) in tetrahydrofuran (40ml) added slowly. After a further 2h the mixture was allowed to warm to room temperature before being poured into ice water (20ml). The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (3 portions of 20ml) and brine (2 portions of 20ml), dried (MgSO₄) and concentrated under reduced pressure to give an
20 oil. Purification by chromatography on silica gel, eluting with petroleum ether / ethyl acetate (90:10) gave 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (456mg) as a red oil.

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde used as starting material in the
25 above preparation was prepared as follows:

A solution of Dess-Martin periodinane (187mg) in dichloromethane (4ml) was treated slowly with a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (100mg) in dichloromethane (4ml) and the mixture stirred for 1h at room temperature.

Diethylether (10ml) was added followed by aqueous sodium thiosulphate solution
30 (10ml) and the mixture stirred for 15 minutes. The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with aqueous

sodium thiosulphate solution (3 portions of 10ml), water (3 portions of 10ml) and brine (2 portions of 10ml), dried (MgSO₄) and concentrated under reduced pressure to give a yellow solid. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (85mg).

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol used as starting material in the above preparation was prepared as follows:

A solution of 3-hydroxy-4-methylbenzyl alcohol (275mg) in dry tetrahydrofuran (15ml) at -78°C was treated slowly with n-butyllithium (1.2ml of a 1.8M solution in hexane) and the mixture stirred for 15minutes before being allowed to warm to room temperature and stir for a further 30minutes. A solution of *tert*-butylchlorodimethylsilane (287mg) in tetrahydrofuran (10ml) was added and the mixture stirred for 16h. Water (20ml) was added and the mixture extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (2 portions of 10ml) and brine (20ml), dried (MgSO₄) and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (390mg).

EXAMPLE 2

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate

Trifluoroacetic acid (0.22mL, 2.95mmol) was added dropwise to a stirred solution of (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate (401mg, 0.82mmol) and dichloromethane (16mL). The mixture was stirred at room temperature overnight. Solvent was removed *in vacuo*, and the residue azeotroped four times with toluene. The colourless oil was triturated with ether to give the title compound as a white solid (181mg, 58%) m.p. 109-113°C. nmr: δ H (500MHz, d₆-DMSO) 2.39 (s, 3H), 3.81 (s, 6H), 3.87 (s, 3H), 6.69 (d, J=12Hz, 1H), 6.74 (d,

J=12Hz, 1H), 6.78 (s, 2H), 7.07 (d, J=8Hz, 1H), 7.28 (d, J=8Hz, 1H), 7.49 (s, 1H), 9.0 (bs, 2H).

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate was prepared as follows:

Di-*tert*-butylphosphoramidite (498mg, 2.00mmol) in dichloromethane (1mL) was added to a solution of (Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (300mg, 1.00mmol), 1*H*-tetrazole (182mg, 2.60mmol) in dichloromethane (3mL) under nitrogen. After 2h, magnesium monoperoxyphthalate hexahydrate (1.24g, 2.00mmol) was added in portions. After stirring for a further 2h, the reaction mixture was partitioned between ethyl acetate and water; the aqueous phase was extracted (ethyl acetate x2); the combined organic extracts were washed (water x2, brine x1); dried (MgSO₄) and concentrated *in vacuo*. Flash chromatography, eluting with 33% ethyl acetate/hexane, gave (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate as a yellow oil (401mg, 82%).

EXAMPLE 3

(Z)-1-(4-fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

This compound was isolated directly from the Wittig reaction between 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-*tert*-butyldimethylsilyloxy-4-fluorobenzaldehyde (340mg) performed in an analogous manner to that of Example 1. There was obtained the title compound (80mg) as a colourless oil. nmr: (300MHz, d₆-DMSO) 3.59 (s, 6H), 3.63 (s, 3H), 6.46 (d, J=12Hz, 1H), 6.48 (d, J=12Hz, 1H), 6.54 (s, 2H), 6.68 (m, 1H), 6.90 (dd, J=8.8, 2.1Hz, 1H), 7.06 (dd, J=11.4, 8.4Hz, 1H), 9.80 (s, 1H).

The following compounds were prepared in an analogous manner to that of Example 1:

EXAMPLE 4(Z)-1-(4-chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

- 5 From (Z)-1-(3-*tert*-butyldimethylsilyloxy-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene (240mg) there was obtained the title compound (121mg) as a colourless oil. nmr: (300MHz, d6-DMSO) 3.59 (s, 6H), 3.63 (s, 3H), 6.49 (m, 2H), 6.54 (s, 2H), 6.71 (dd, J=8.2, 0.9Hz, 1H), 6.93 (d, J=0.9Hz, 1H), 7.25 (d, J=8.2Hz, 1H), 10.11 (bs, 1H).m/e 320 (M+).

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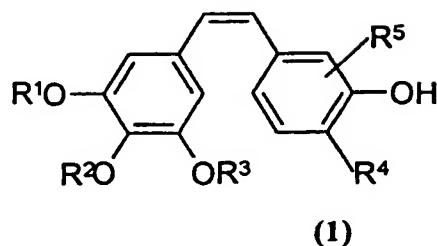
EXAMPLE 5(Z)-1-(4-ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

- From (Z)-1-(3-*tert*-butyldimethylsilyloxy-4-ethylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (926mg) there was obtained the title compound (208mg) as a white solid m.p. 105-107°C, nmr: δ H (300MHz, CDCl₃) 1.02 (t, J=7.6Hz, 3H), 2.6 (q, J=7.5Hz, 2H) 3.7 (s, 6H), 3.8 (s, 3H), 4.6 (bs, 1H), 6.4 (d, J = 12Hz, 1H), 6.5 (d, J = 12 Hz, 1H), 6.5 (s, 2H), 6.7 (s,1H), 6.8 (d, J= 7.6Hz, 1H), 7.0 (d, J = 7.6Hz, 1H).

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CLAIMS:

1. A cis-stilbene of formula



Wherein:

- 10 R^1 , R^2 and R^3 are each independently alkyl,
 R^4 is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo,
 R^5 is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo,
or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof.
- 15 2. A cis-stilbene according to claim 1 wherein
 R^1 , R^2 and R^3 are all methyl.
3. A cis-stilbene according to claim 2 wherein
 R^5 is hydrogen and R^4 is alkyl or halo.
- 20 4. (Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene.
5. A prodrug of a cis-stilbene which is an carboxylic ester, phosphate ester,
sulphate ester or carbonate of a cis-stilbene as claimed in any one of claims 1 to 3.
- 25 6. A prodrug of a cis-stilbene which is a phosphate ester of a cis-stilbene
according to claim 1.

7. A prodrug according to claim 5 which is a dihydrogen phosphate ester.
8. (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate.
- 5 9. A composition for use in the treatment of neovascularisation which composition contains an effective amount of a cis-stilbene according to any one of claims 1 to 4 or a prodrug thereof according to any one of claims 5 to 8.
- 10 10. Use in the preparation of a composition for the treatment of neovascularisation of a cis-stilbene as claimed in any one of claims 1 to 4 or a prodrug thereof according to any one of claims 5 to 8.